THE MEDICAL LETTER

a non-profit publication

on Drugs and Therapeutics

Published by Drug and Therapeutic Information, Inc., 136 East 57th Street, New York 22, New York

Vol. 1, No. 7 April 17, 1959

SINGOSERP

Continuing experience with reserpine and other rauwoloid alkaloids makes it increasingly clear that their relatively slight hypotensive effects are obtained at the price of frequent and sometimes serious side effects. Now syrosingopine (Singoserp-Ciba), a new rauwolfia derivative, is being promoted as an antihypertensive agent practically free of untoward side effects. Despite the claims made for it, at this point Singoserp does not appear to be a significant contribution to the treatment of hypertension. (A review of rauwolfia products in general is now in preparation.)

The earliest clinical judgment on syrosingopine, prior to the marketing of Singoserp, was expressed by Robert Wilkins (N. E. J. of Med., 21:1026, 1957), who reported that this drug "may be less sedative or tranquilizing than reserpine, but in general it is also less hypotensive... it is the least effective of the pure alkaloids, producing sustained hypotension in only 1/3 to 1/2 of reserpine responders." More recent evidence does not alter the judgment that syrosingopine is not a very effective drug.

SIZE OF DOSE - Despite the many clinical trials of the drug, there have been few published reports. One small non-controlled series has been fully published (Barbour, et al., Amer. J. of Cardiology, 3:220, 1959), and another has been published in abstract form (Darvil, Clinical Research, 6:232, 1958). These reports indicate that the dose of syrosingopine may have to be four to ten times (up to 20 mg.) the dose of reserpine. (The manufacturer of Singoserp recommends a maintenance dosage of 0.5 to 3 mg. daily.) It was found that patients with mild hypertension were most benefited by Singoserp. Mild hypertension frequently responds to reassurance and mild sedatives, as well as to placebos. The very limited published evidence leaves room for doubt that Singoserp in the recommended doses would be appreciably more effective than a mild sedative or even a placebo.

Side effects, including occasional mental depression - a frequent side effect of other rauwolfia products - were noted in about 20% of the patients studied by Barbour, et al. The incidence of side effects in cases treated with other rauwolfia products in other trials is considerably higher. The number of cases in the Barbour series was so small, however, that no significance can be attached to the figures, particularly in the absence of adequate controls.

The cost to the patient of 1-mg. Singoserp tablets is about $7 to $8 a hundred (about 10¢ a tablet in smaller quantities). The price of .25-mg. reserpine tablets is about $2.50 to $4 a hundred. If the physician prescribes reserpine under the trade name of Serpasil (Ciba), the price will be about $6.50 to $7.50 a hundred.

SENOKOT

If volume of promotion and multiplicity of citations could be accepted as a measure of effectiveness, Senokot (Purdue-Frederick) would be the laxative of choice for all cases of constipation requiring treatment. Senokot is offered as the "standardized concentrate of total active principles of Cassia acutifolia pods." In other words, it is the familiar senna, but the material is derived from the pods rather than from the ground leaf, which is official Senna NF. Like other so-called emodin cathartics, such as cascara and aloe, senna stimulates the large bowel through Auerbach's plexus as well as directly, and serves as a mild, slow-acting cathartic with a modicum of cramps or griping.

Senna itself is a useful cathartic, though it has little, if anything, to recommend it over cascara, which is considered to be the least griping of the emodin cathartics. If Senokot successfully eliminated griping by the substitution of the pods for the leaves as the source of its active elements, that would be an important gain, but griping is not abolished with Senokot. One of the authors cited in Senokot literature (A. S. Duncan, British Med. J., 5016:439, 1957) reported that "of patients who had a positive [laxative] response within 24 hours, 10 (12.5%) in the cascara series and 22 (17.2%) in the Senokot series experienced gripes."

ADVANTAGE OF SENOKOT - Senokot does offer the advantage that, unlike Senna NF, it is a standardized, stable preparation. Because of the deterioration of senna over a period of time, relatively large doses may sometimes be required. Since patients are not standardized, however, and vary greatly in their response, the effective dosage of either Senokot or senna must be determined by trial, and in any one patient the response to the drug varies from time to time.

The wide range of dosage requirements is pointed up in another report cited in Senokot promotion (T. A. Lamphier and R. Ehrlich, Amer. J. of Gastroenterology, 27:381, 1957), which shows that the required dosage of Senokot ranged from less than one up to four teaspoonfuls, though the manufacturer suggests a maximum of two teaspoonfuls. It is also well known that tolerance to a laxative drug often develops, making it relatively ineffective after a time and requiring larger doses or the substitution of another drug.

Reliable evidence that Senokot is superior in effectiveness when compared with adequate doses of senna, or is freer of griping effects, has not been forthcoming. Where economy is important, therefore, there is no reason for burdening a patient (or a hospital) with the greater expense of this product. While 4 oz. of Senokot granules cost about $3 to $3.50, a like amount of compound senna powder (compound licorice powder), which is used in roughly the same dosage, costs about 50¢ to 65¢.

OPHTHALMIC STEROID PREPARATIONS AND MIXTURES

Over 30 topical eye preparations containing steroids are offered to physicians for use in ocular infections, allergies and injuries. Most of these preparations are mixtures of steroids with one or more antiseptics, antihistamines, antibiotics or sulfa drugs. It is easy to get the impression from the advertisements for such preparations that any acute or chronic disorder of the eye can be successfully managed with steroid or steroid-combination eye drops or ointments without the need for an accurate diagnosis. Any such impression is a dangerous one, for topical steroids can cause severe impairment of vision and even blindness.

Serious herpetic infection of the cornea is now one of the chief causes of corneal disease in this country; and the use of steroids, especially topically, in herpes inflammation of the cornea can cause marked spreading of the infection. The consequence of such use is likely to be an extensive ulcer involving the entire thickness of the cornea, and ending in serious visual impairment or blindness. To make matters worse, the herpes simplex virus can lie dormant in the body (especially in persons prone to herpes labialis), and the use of topical (or oral) steroids for other conditions may trigger the initiation of herpetic inflammation of the cornea. Not only can topical steroids aggravate or induce a herpetic infection, but they have also been suspected of encouraging infections of the cornea by fungi and Pseudomonas (pyocyaneus) organisms.

Despite the risks, however, topical steroids are valuable drugs in the hands of ophthalmologists for the treatment of severe inflammatory reactions of allergic or toxic origin and in sympathetic ophthalmia. Ophthalmic steroids are also useful in acute bacterial infections in which the inflammatory reaction appears excessive and may be destructive by itself. But steroids must be used with discrimination even by ophthalmologists, and only for clearly indicated conditions.

STEROID-ANTIHISTAMINE COMBINATIONS - Metreton Ophthalmic Suspension (Schering) is perhaps the best known example of a steroid-antihistamine combination advocated for use in ocular allergies. It consists of 0.2% prednisolone and 0.3% chlorprophenpyridamine (Chlor-Trimeton). It is claimed that the antihistamine "notably enhances and complements the antiallergic properties of the prednisolone," and that "its inclusion therefore reduces the therapeutic concentration of the steroid necessary for effective treatment."

These claims are not supported by the facts. According to F. H. Theodore and A. Schlossman (Ocular Allergy, Williams and Wilkins Company, 1958), the topical use of antihistamines in ocular allergy is ineffectual. Beneficial effects from steroid-antihistamine combinations are entirely due to the steroid. Local antihistamines are not only ineffectual, but they may themselves cause allergic or irritating conjunctival reactions in the same way that antihistamine ointments have been responsible for allergic skin reactions.

In ordinary allergic inflammatory reactions caused by pollens, dust and other allergens, instead of a steroid or an antihistamine, a vasoconstrictor solution such as epinephrine 1:5000, phenylephrine (Neo-synephrine) 1/8%, Naphazoline NF (Privine Ophthalmic) or tetrahydrozoline (Visine) should be prescribed.

ANTISEPTIC, SULFA AND ANTIBIOTIC STEROID COMBINATIONS - Numerous combinations of steroids and anti-infectives are available, but there is little justification for the use of any of them. Minor bacterial infections of the eye such as blepharitis, sty and conjunctivitis are self-limited and mild, and clearly do not justify the risks of steroid therapy. In place of a combination of a steroid and an anti-infective, a simple, antibacterial topical preparation should be employed. Useful and safe preparations for such minor infections include: a 5% solution of sodium propionate (Propion Ophthalmic-Wyeth); zinc sulfate-1/5% aqueous solution; or yellow oxide of mercury ointment-1%. Eye solutions or suspensions are generally preferred to ointments because the latter are messy and tend to interfere with vision. If these mild antiseptics are not effective in 24 to 48 hours, a sulfa ophthalmic solution such as 4% sulfisoxazole (Gantrisin Ophthalmic-Roche) or sodium sulfacetamide (Sulamyd Ophthalmic, 10%-Schering) may be tried. Major eye infections - those which threaten sight - demand immediate care by an ophthalmologist, who will employ bacterial culture and sensitivity tests to assist in selecting an appropriate antibiotic.

The treatment of eye infections with steroid-combination drugs is almost always undesirable. The use of such combinations where only one drug is needed invites unnecessary allergic reaction or chemical irritation. Furthermore, the suppression by a steroid of the inflammatory reaction due to infection may impair both the natural defenses of the tissues and the action of the anti-infective itself; meanwhile, with the infectious process unabated, the eye appears relatively uninflamed and the physician is lulled into a false security.

There are a few - and only a few - occasions where the use of the combination (or separate steroid and antibiotic) would be indicated: where both bacterial infection and either allergy or toxicity are known to play a role, as in phlyctenulosis and infectious eczematoid staphylococcus dermatitis, and in those rare instances in which bacterial infection produces an exaggerated or excessive inflammatory response; in such instances, the antibiotic can help control the infectious process while the steroid reduces the inflammatory reaction.

Ophthalmic steroids are highly useful medications. But few have a greater potential for misuse; and ophthalmic steroid combinations almost invite misuse.

INDEX TO THE MEDICAL LETTER - Vol. 1, No. 1 - No. 6, pp. 1-24

THE MEDICAL LETTER ON DRUGS AND THERAPEUTICS is published fortnightly by Drug and Therapeutic Information, a non-profit corporation, 136 E. 57th St., New York 22. N. Y. Second-class postage paid at New York, N. Y. The subscription fee is $12.50 per year ($6.25 for residents, internes and students).